Vaccine 39 (2021) 1025–1026

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

# Development of vaccines for influenza disease: Opportunity costs of the COVID-19 pandemic

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Cases of influenza reported by clinical and public health laboratories declined drastically in the United States from late March 2020 onward [1] (Wiemken application available at https://surveillance.shinyapps.io/covidsyndromic). This reduction, which is temporally consistent with the tail end of influenza season in North America, was more pronounced in the 2019/2020 influenza season than in previous years [2], coinciding with the adoption and implementation of successful 2019 Coronavirus Disease (COVID-19) prevention measures across the United States.

A similar pattern occurred in the Southern Hemisphere, early in the influenza season. At that time, influenza rates were significantly lower than average, likely due to interventions to prevent COVID-19 [3]. Since these interventions target both influenza and SARS-CoV-2, they could be seen as contributing factors to the below-average levels of reported influenza. Since the end of the influenza season in the Southern Hemisphere, reports have suggested historically low caseloads [4]. Using data from the World Health Organization Global Influenza Surveillance and Response System [5], for weeks 14 through 36 in years 2018, 2019, and 2020, we calculated influenza positivity rates which suggested dramatic declines from 14.3%, to 11.0% to 0.21%, respectively. Since the influenza season in the United States is only beginning at the time of writing (December 2020), data for the 2020/2021 influenza season are as of yet unavailable.

Low levels of influenza activity early in an influenza season compromise necessary data structures quantitatively and qualitatively, which in turn may translate into significant opportunity costs (e.g. consequences or loss of benefit due to the outcomes of a particular intervention) in the protection of certain influenza-vulnerable populations in the subsequent seasons. In this manuscript, we characterize a major opportunity cost of these short-term interventions for COVID-19 prevention and their impact on influenza in younger and other vulnerable populations.

Although there have been notable developments in recent years such as high dose, adjuvant, cell-based/recombinant, and the quadrivalent vaccines [6], the most common manufacturing process for influenza vaccines maintains a reliance on egg-based techniques to produce an inactivated vaccine. This process has been observed for over seven decades without major changes to the status quo [7]. The strains used in the main influenza vaccines for a particular hemisphere are predicted *a priori* based on dominant transmission and other viral and epidemiologic factors in the opposing hemisphere early in their influenza season [8].

Currently, the Northern Hemisphere 2020–2021 vaccine candidate viruses have already been selected and vaccine is being provided to the public [9]. Therefore influenza scarcity in the Southern Hemisphere did not pose significant difficulties for the 2020–2021 Northern Hemisphere influenza season. Regardless, the process of identifying viruses as candidates is imperative during the early stages of influenza season for two reasons. First, the process of growing influenza viruses using the egg-based approach is inherently time-consuming. And second, some viruses grow poorly, particularly the H3N2 strains, which traditionally result in the most severe influenza seasons with the highest pneumonia and influenza-associated mortality [10]. However, it is unknown as to how much circulating virus is necessary to adequately predict an effective influenza vaccine. This topic deserves attention in future studies.

Early availability of these data points originating in an opposing hemisphere is but one factor in optimal seasonal vaccine development for the subsequent Northern Hemisphere influenza season (and vice versa in the subsequent season for the Southern Hemisphere). Influenza viruses are capable of mutating rapidly, with the possibility of different strains taking over later in the season or undergoing antigenic drift between winter seasons in the Southern and Northern Hemispheres, reducing vaccine effectiveness. Nonetheless, it is clear that interventions to reduce COVID-19 have also been successful for reducing influenza disease. The opportunity cost of these interventions, which will undoubtedly continue into the Northern Hemisphere for the 2020–2021 influenza season is the likelihood of greatly reducing the window of opportunity for the use of proxy data points in the development of influenza vaccines for the 2021 season in the South. In turn, this exposes

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https://doi.org/10.1016/j.vaccine.2021.01.014

populations to a potentially acute influenza seasons, likely coinciding with substantial COVID-19 in the absence of widespread immunity. This possibility could be tempered if antigenic drift slows concurrently with the slowing of influenza transmission, however. This is a critical aspect of influenza viral evolution that should not be overlooked during this unique time.

The combination of COVID-19, as well as heightened levels of influenza disease, would be devastating in any hemisphere. Because severe morbidity and mortality for COVID-19 and influenza only partly overlap by age group, it should be underscored that in the event of a severe influenza season, the opportunity costs referenced above are likely to translate into a heightened overall public health toll for younger populations. So far in the COVID-19 pandemic, data suggest that infant and pediatric populations have been less affected than elderly or immunocompromised populations [11,12]. Influenza infection, by contrast, is typically taxing on very young and elderly populations [13,14]. These groups lead to major concerns when vaccines are not well matched to circulating influenza strains. In the event of SARS-CoV-2 transmission with concomitant influenza transmission and a poorly matched influenza vaccine, interventions for respiratory disease transmission prevention will be even more critical. At this point, school closures would likely be widespread and mandatory in order to protect the young from influenza disease and death. In this combined transmission scenario, the burden to hospitals and healthcare systems may also be considerable higher than during the initial peak of COVID-19 in the spring of 2020, and now in December of 2020. The necessary COVID-19 prevention interventions in the Southern Hemisphere during the 2021 influenza season may subsequently reduce the ability to identify the ideal influenza vaccine candidates for the 2021/2022 season in the Northern Hemisphere, and so-forth until an effective SARS-CoV-2 vaccine is readily available. This pattern will be difficult to break until a substantial portion of the global population has been adequately immunized to SARS-CoV-2. A return to normal (e.g. limited) prevention for respiratory viruses will likely lead to a resurgence of influenza transmission and a return to the pre-COVID status quo.

The issues associated with severe influenza seasons coinciding with poorly matched vaccines are many. Morbidity and mortality may be extremely high, potentially approximating some locations experience with COVID-19 outcomes. This was exemplified in 2017/2018 influenza season when a poorly matched (40% effectiveness) vaccine strain resulted in historically high morbidity and mortality [15]. This resulted in nearly triple the deaths due to influenza typically seen in the US annually. It takes little imagination to conceptualize a scenario with an extremely low effectiveness vaccine and a severe influenza season. Luckily, there may be some cross reactivity assisting in effectiveness even in these scenarios [16].

Even in the absence of more waves of COVID-19, the irreversibility of early-stage decision-making processes regarding the development of influenza vaccines may nonetheless result in a heightened burden to healthcare systems, while leaving younger populations particularly exposed to influenza infection. As mentioned previously, this will necessitate a more lengthy and rigorous intervention period even when a SARS-CoV-2 vaccine is likely to be introduced early in 2021. These interventions will be necessary to prevent both COVID-19 and influenza disease in all age groups.

Most importantly, the data gaps, as well as the associated research and development problems caused by the late and below-average onset of the influenza season in the Southern Hemisphere, highlight longstanding inefficiencies in influenza and pandemic preparedness. The decades-old reliance on fallible vaccine technology in this area, the systematic defunding of public health over many decades in the United States, and the disruptive effects to vaccine research and development brought about by concomitant outbreaks of infectious diseases, suggests that greater policy emphasis should be placed on the funding and testing of novel vaccine technologies. These, if successfully developed, may reduce the need for proxy data and improve our ability to make rapid modifications to vaccines before wide dissemination, reducing or eliminating the opportunity costs outlined above. This in turn, could reduce the reliance on interventions which are socially, mentally and economically damaging to humanity.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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